PRM68
HEALTH ECONOMIC ANALYSIS OF PNEUMOCOCCAL VACCINATION – EXAMPLE FROM BULGARIA
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OBJECTIVES: To evaluate cost-effectiveness of pneumococcal vaccination of children with 10-valent (PHiD-CV) compared with 13-valent pneumococcal conjugate vaccine (PCV-13). **METHODS:** A Markov cohort model which simulates in a Bulgarian birth cohort the disease process of invasive disease (ID) (meningitis and bacteremia), community acquired pneumonia (CAP), and acute otitis media (AOM) over life-time caused by S. pneumoniae and non-typeable Haemophilus Influenzae (NTHi). The cohort model essentially considers the perspective of the health care payer. Bulgarian specific epidemiological and demographic data and data from other country sources were obtained for the model. Base case assumptions include estimates of pneumococcal and NTHi infection rates as well as vaccine efficacy based on published literature, 94% vaccine coverage, herd protection and a (3+1) vaccination schedule. One-way sensitivity analyses performed to assess the impact of changes in key model assumptions. **RESULTS:** PHiD-CV and PCV-13 are projected to prevent 29.4 and 29.9 cases of invasive diseases respectively and 437 and 434 bacteremia hospitalizations respectively . PHiD-CV in comparison with PCV-13 is projected to prevent additional 9393 cases of AOM, 426 myringotomies and 2801 GP visits. Vaccinating a birth cohort with PHiD-CV is expected to generate 41 more QALYs compared to PCV-13. The estimated total savings for health care system are 1.77 mil Euro. The PHiD-CV is dominant in comparison with PCV-13. Sensitivity analyses indicate that GP visits for AOM and efficacy vs. AOM due to Streptococcus Pneumonia non-Vaccine Types Sp nVT have biggest impact on results. **CONCLUSIONS:** Overall, PHiD-CV is expected to have betterI impact and under the given assumptions, PHiD-CV dominates PCV-13 because it also has a larger cost offsets.

PRM69
CORRELATING COST EFFECTIVENESS OUTPUT WITH PATIENT LEVEL DATA INPUT VIA THE IMS CORE DIABETES MODEL (CDM)
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OBJECTIVES: Analysing patient level data (PLD) within cost-effectiveness (CE) models offers the potential to better understand patient profiles associated with greatest health economic benefit. The objective of this study was to contrast the application of average treatment efficacy profiles compared to patient level treatment efficacy in assessing the CE of insulin glargine (IG) versus Neutral protamine Hagedorn (NPH) in Type 2 diabetes mellitus (T2DM) **METHODS:** This study used the IMS Core Diabetes Model (CDM), a validated and established diabetes model to evaluate the CE of switching to IG from NPH using published effectiveness data from a large population based cohort. Average HbA1c reduction after switching from NPH was -0.18% and weight gain was 0.5kg. Annual diabetes specific therapy cost was £573 (IG) versus £320 (NPH). A PLD extract was obtained from NHANES and the CE of IG versus NPH assessed applying (a) overall mean treatment effects (MTE) and (b) baseline HbA1c, BMI and sex adjusted treatment effects (ATE). Costs (2012 UK£) and benefits were discounted at 3.5%. **RESULTS:** For the MTE and ATE scenarios, the incremental cost effectiveness ratio (ICER) was £28,925 and £57,279 respectively. For MTE scenario, 765 (41.1%) of subjects were CE at the £20,000 willingness to pay (WTP) and 47 IG subjects (6.1%) were both cost saving with increased health benefit. Using ATE, 525 (28.2%) were CE at the £20,000 WTP threshold with 164 (31.2%) of IG subjects identified as both cost saving with increased health benefit. The odds ratio (OR) of being both cost saving with greater health benefit was significantly associated with age, OR=0.89(0.87-0.93) and baseline HbA1c, OR=6.11 (4.64-8.03). **CONCLUSIONS:** The identification of patient characteristics associated with greater potential for health gain and reduced cost is an important goal. The analysis of PLD alongside simulation model output provides an additional mechanism for informing health care decision-making.

PRM70
COMPARISON OF MARKOV AND DISCRETE EVENT SIMULATION MODELING TECHNIQUES WITH APPLICATION TO COST EFFECTIVENESS ANALYSES
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OBJECTIVES: To assess the bias introduced to absolute costs, absolute QALYs and the incremental cost effectiveness ratio (ICER) associated with Markov models, compared with discrete event simulation (DES) models. To investigate how such biases are a function of cycle length and half-cycle correction. **METHODS:** A hypothetical three health state model was constructed using both Markovian and DES approaches. Costs and utility were assigned to each health state and the ICERs between two treatment strategies were estimated. Six Markov models using different cycle lengths (1 month, 3 month, 1 year), and with and without half cycle correction were constructed. Differences in the absolute costs and QALYs generated between each Markov model were compared with the DES approach and the ICERs generated by each model were compared. **RESULTS:** Markov model simulation was shown to introduce biases in the absolute costs and QALYs when compared with a DES approach. The bias was related to the duration of the time cycle with the results converging to the DES values as the time cycle was reduced. The initial bias in cost fell from 14% to less than 1%; QALY bias was consistently below 1%. The ICERs show bias between 2.4% and 9.6% when using a 1 year cycle and between 0.6% - 5.4% when using a 1 month cycle. The half-cycle correction reduced absolute bias between 2% - 10%, the ICERs were not affected. The time cycle duration was the primary parameter in reducing bias. **CONCLUSIONS:** Markov models introduce bias due to the simplifying assumptions of fixed cycle length and half cycle correction; DES models do not suffer the same biases. It is suggested that when the ICERs produced are close to the Willingness to Pay threshold, Markov models should be analyzed with shorter cycle length or a DES approach adopted to ensure conclusions are robust.

PRM71
MODEL-BASED ECONOMIC EVALUATIONS IN ALZHEIMER'S DISEASE : A REVIEW OF MODELING METHODS
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OBJECTIVES: To review the modeling-based economic evaluations (MB2E) of acetylcholinesterase inhibitors (ACE) and memantine (MEM) used in the field of Alzheimer's disease (AD). **METHODS:** A systematic literature search was carried out based on several electronic databases such as Medline or the Cochrane Library up to November 2012. Modeling frameworks used to depict the natural history of AD and incorporation of treatment effects were qualitatively described and compared. **RESULTS:** More than thirty MB2E were identified with several local adaptations based on ten original modeling frameworks. First published MB2E were either Markov state-transitions models or partition failure time survival models while most recent MB2E relied on discrete events simulations. The hallmark of the disease, the cognitive dimension, was first introduced to model the disease progression mainly based on the Mini Mental State Examination (MMSE) scale. The two other fundamental-functional and behavioral-dimensions were taken into account as a second step. Models relied on distinct clinical milestones and risk equations to extrapolate intermediate clinical endpoints from clinical trials (mainly on cognition and function) into long-term final endpoints. These latter were delay in severity, loss of patient autonomy, institutionalization, burden of care and quality-adjusted life years. Differences occurred as well on the way inter-patient heterogeneity was incorporated with a trend towards more micro-simulations technics. Eventually, predictors and inter-relations between the several dimensions of the natural history of the disease seemed not to be fully captured in the model structures with challenging needs to assess the resulting potential biases. **CONCLUSIONS:** Advanced modeling methods in the field of AD were being introduced to better capture the continuous, progressive and multivariate natural history of AD. Further work is warranted given the emerging early diagnosis technics, neuropathological biomarkers and targeting therapies.

PRM72
THE COST-EFFECTIVENESS OF SEQUENTIAL FIRST- AND SECOND-LINE TREATMENTS IN METASTATIC RENAL CELL CARCINOMA USING REAL-WORLD DATA AND A PATIENT-LEVEL SIMULATION MODEL
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OBJECTIVES: Previous cost-effectiveness analyses of targeted therapies in metastatic renal cell carcinoma (mRCC) have been based on randomised trials and evaluate just one single treatment-line. The aim of this study was to estimate the real-world cost-effectiveness of sequential first- and second-line treatments for patients with mRCC using a patient-level simulation (PLS) model. **METHODS:** Based on patient-level data from a Dutch population-based registry, a PLS model was developed that comprised entities (i.e. patients with mRCC), attributes assigned to the entities (i.e. prognostic factors), and events (i.e. second-line treatment or death). Patients were repeatedly simulated from the model and time-to-event was estimated using a lognormal distribution. A separate sampling process was used to determine which type of event occurred. Time to death following second-line treatment was modelled using a Weibull distribution. Lifetime health care costs were modelled using patient-level data from the registry. **RESULTS:** In current daily practice, 50% (341/686) of patients did not receive any targeted therapy and 42% (291/686) received sunitinib as first-line therapy. In the second line, 31% (33/107) were treated with sorafenib and 31% (33/107) with everolimus. Mean overall survival (OS) was 13.6 months and mean costs were €69,622 for all patients. In a strategy where all patients are treated according to clinical guidelines, mean OS was 15.2 months and costs were €91,059. This meant an increase in OS (1.6 months) and costs (€21,437) compared to current practice, with an incremental cost-effectiveness ratio of €159,107 per life-year gained. Probabilistic sensitivity analyses showed the robustness of these results. **CONCLUSIONS:** A complete disease model and real-world data are essential in estimating real-world cost-effectiveness. Our PLS model allows comparisons between treatment strategies spanning multiple treatment lines, which will ultimately help to reveal the optimal strategy. For example, guidelines-based treatment appears to increase both OS and costs compared to current daily practice.

PRM73
THE ROLE OF SIMULATION MODELING IN PLANNING LONG-TERM CLINICAL TRIALS IN TYPE 2 DIABETES
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OBJECTIVES: Long-term cardiovascular outcomes studies are routinely undertaken to demonstrate safety in all new diabetes therapies. Given that diabetes models are extensively validated to contemporary outcomes trials they offer the potential to inform on design of new trials. The objective of this study was to use an established diabetes model to explore the relationship between levels of glycaemic control, major adverse cardiovascular events (MACE) and sample size. **METHODS:** The IMS CORE Diabetes Model (CDM) a validated and widely used simulation model was initiated with patient level data (PLD) drawn from NHANES. The model was run with a five-year time horizon and the sample sizes required to detect a difference in MACE (defined as myocardial infarction, stroke or CV death) at the 5% level as a function of change in HbA1c evaluated. **RESULTS:** PLD from NHANES was available on 1853 subjects with mean (SD) age 63.6(12.1) years, 53% male, duration of diabetes 9.6(8.5) years, baseline HbA1c 7.4% (1.8), systolic

blood pressure 134.9mmHg (22.0) and total cholesterol of 189.8 mg/dl (48.7). The expected five-year cumulative MACE event rate was 9.2% and HbA1c reductions of 0.5%, 1.0% and 1.5% produced relative risk reductions of 7.5%, 9.0% and 10.6% respectively. At the 5% level, the number of patients required to detect a significant reduction in MACE events was 17,786, 11,758 and 1,912 for HbA1c reductions of 0.5%, 1.0% and 1.5% respectively. On average, each half-unit change in HbA1c required an additional 7,937 subjects to detect a significant difference in MACE event rate. **CONCLUSIONS:** Given the requirement to extensively validate health economic models to contemporary outcomes studies it is an obvious extension to use these models to inform on the design of clinical trials. These models offer considerable flexibility in the evaluation of sample size requirements in terms of expected changes in modifiable risk factors.

PRM74

DEVELOPING REALISTIC PATHWAYS IN COST-EFFECTIVENESS MODELS FOR PSORIASIS: WHAT TO DO WHEN A BIOLOGIC FAILS

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OBJECTIVES: Clinical studies indicate switching to a second biologic or combination therapy with an immunosuppressant after failure of first biologic can be effective in patients with moderate to severe plaque psoriasis not responding to the first biologic. **METHODS:** A systematic literature review was performed to assess treatment pathways included in cost-effectiveness (CE) estimates of biologic treatments of moderate to severe psoriasis and compare these pathways with those recommended in psoriasis treatment guidelines. **RESULTS:** Twenty-one CE modeling studies were identified. Of these 10 estimated incremental cost per responder for >=1 biologics over time horizons varying from 12 weeks to 18 months. Treatment pathways were considered not relevant in these studies. In 11 studies with time horizons up to 10 years where treatment pathways were considered, 5 studies included a switch to non-systemic therapy or best supportive care after failure of the initial biologic. In 6 of 11 studies, failure of the initial biologic was followed by monotherapy with a second-line biologic - one of the recommendations in current treatment guidelines. In only 1 of 6 studies that considered treatment sequencing was the efficacy of the second-line biologic adjusted downwards compared to first line treatment. None of the cost-effectiveness analyses included dose titration with the first-line biologic or combination therapy with a biologic plus methotrexate or phototherapy after failure of the first-line biologic as recommended in some treatment guidelines. **CONCLUSIONS:** In most long term CE studies, failure of the first biologic was followed by biologic monotherapy of the second, without efficacy adjustment. Some treatment guidelines support dose titration or combination treatment after failure of a first-line biologic. Nevertheless, these options were not included in the published CE models with time horizons up to 10 years. For decision makers there may be a need for more extensive models where such strategies are allowed.

PRM75

DECISION ANALYTIC MODELS USED IN ESTIMATING THE COST-EFFECTIVENESS OF DRUG-ELUTING STENTS VERSUS BARE-METAL STENTS: A SYSTEMATIC REVIEW

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OBJECTIVES: Drug-eluting stents (DES) and bare-metal stents (BMS) are both used widely in percutaneous coronary interventions. However, cost-effectiveness analyses of DES versus BMS conflict about whether the reduction in repeat revascularizations of DES versus BMS offsets the initial higher treatment costs of DES. A systematic review was performed to examine whether modelling methods influenced the cost-effectiveness of DES versus BMS. **METHODS:** We reviewed modelling studies published until January 2012 that compared the costs and consequences of DES versus BMS. General information (e.g. funding) and modelling methods used, related to the framing of the economic evaluation (e.g. population and intervention characteristics, time horizon) and parameterisation of the models were extracted from the relevant studies for each of the individual analyses performed in the studies. Associations between these characteristics and the incremental costs and effectiveness were explored using regression analysis. We also examined whether the results were associated with the quality of the models based on the Philips et al. (2006) checklist. **RESULTS:** Fifteen eligible studies accounted for 498 separate analyses, in which the incremental cost-effectiveness ratios ranged from DES being dominated by BMS to DES being dominant. The most important predictors significantly associated with these differences were several population and procedure characteristics, funding and assumptions concerning stent efficacy. The results and conclusions of individual studies corresponded with the findings of this meta-level systematic review. Overall quality of the models was moderate (55%±17%) and significantly negatively associated with repeat revascularizations avoided. **CONCLUSIONS:** Models are important to obtain valid estimates of the cost-effectiveness of DES versus BMS, and framing decisions (e.g. time horizon) and quality of the models both influence incremental costs and effects. The most influential parameters are identified with this systematic review and we showed the need of examining those parameters and of performing a quality check when interpreting the results.

PRM76

EXPLORATORY STRUCTURAL EQUATION MODELS: A SIMULATION STUDY EXPLORING GEOMIN AND TARGET ROTATION TECHNIQUES ON VARIATIONS OF ESEM MODELS

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OBJECTIVES: This simulation study evaluates the impact of Geomin and Target rotation criteria on factor loading matrices in the recently developed exploratory structural equation models (ESEM), a method that can be considered a strong alternative to the exclusive use of exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) in patient related outcomes measurement. By combining the steps of EFA and CFA in one unified approach, ESEM saves significant time and effort usually invested in separate iterations of EFA and CFA. **METHODS:** One hundred replications of ESEM models were carried out for variations of sample size and latent factors. *Simulation study 1* examined the behavior of ESEM parameter estimates by changing the values of rotation constant (0.01, 0.001 and 0.0001) in Geomin rotation for a *three-factor single group* model and for N=300 and 1000. Simulation study 2 evaluated the behavior of ESEM parameter estimates for multi-group models using three- and four-factor models for N=150 and 500 per group. Bias, Mean Square Errors (MSE) and standard errors were used to evaluate accuracy of parameter recovery. Item parameters were generated from 27 items belonging to a pilot graduate creativity instrument. **RESULTS:** For study 1, Geomin rotated parameter estimates of factor loadings, means and covariances produce higher MSEs than the follow up Target rotations. In study 2, the parameter estimates for ESEM Geomin show small sample size bias for some parameters while the standard errors produced correct coverage for all parameters under Target rotation method for large N=500 per group. **CONCLUSIONS:** Overall, there was accurate recovery of parameter estimates in the smallest sample of 300 especially in the multi-group models specifically when Geomin rotations were employed. This bodes well for analysis of real data and for the study of measurement invariance across groups. Future studies could include the examination of number of items affecting recovery of parameter estimates.

PRM77

METHODOLOGICAL APPROACHES FOR MODELING CARDIOVASCULAR EVENTS IN COST-EFFECTIVENESS ANALYSES BASED ON OUTCOME TRIALS

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OBJECTIVES: Historically, cardiovascular (CV) endpoints, including myocardial infarction and stroke, have often been included indirectly in cost-effectiveness analyses (CEA) based on surrogate endpoints from clinical trials, such as cholesterol levels, blood pressure or glycemic control. With the availability of outcomes trials sufficiently powered to show differences in CV endpoints, there is an increasing need to incorporate these data directly into CEA. This study investigated approaches available in the published literature for modeling CV endpoints directly based on outcomes data. **METHODS:** A systematic review of cost-effectiveness models for cardiovascular interventions published in the past 5 years was conducted in PubMed and Embase using a predefined search strategy. Only studies in English language directly integrating trial data on CV endpoints from randomized clinical trials were considered. For each study that met the inclusion criteria, clinical input characteristics and the modeling approach were summarized and evaluated. **RESULTS:** Twenty-three papers were identified for final review, including studies of antithrombotic, heart failure, and lipid lowering therapies. Methodologically, decision trees, Markov models (cohort and individual patient), discrete event simulations as well as hybrids of these approaches were used. Event rates were incorporated either as constant rates, time-dependent risks, or risk equations based on patient characteristics. Although potentially more accurately reflecting the trial data, risks dependent on time and/or patient characteristics were only used where feasible (major event rates >1%/year) and practical (models with fewer than seven health states). Models incorporating data from infrequent events or with numerous health states generally preferred constant event rates. **CONCLUSIONS:** When the risk of CV events is low and/or the disease state is explicitly modeled in detail, constant events rates were most common. For heterogeneous populations or when CV event risk is high, simpler model structures were generally accompanied by patient- or time-dependent event rates where permitted by the available data.

PRM78

TWO-WAY SENSITIVITY ANALYSIS: SHOWING THE IMPACT OF CORRELATED PARAMETERS IN COST-EFFECTIVENESS ANALYSES

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OBJECTIVES: Correlated parameters are a common feature in economic models, but no standard sensitivity analysis (SA) exists to show their impact on cost-effectiveness. The one-way SA only varies one parameter at a time and ignores correlation while the probabilistic SA is typically used to address overall uncertainty. The objective of this study is to propose a standard method for visualising the impact of one variable consisting of two correlated parameters in cost-effectiveness analysis. **METHODS:** A model evaluating the cost-effectiveness of a cancer product was used. Using the Cholesky decomposition, 1,000 correlated random draws were generated from the distributions of the intercept and slope of a linear function determining survival in the model. Each pair was inputted in the model to yield the percentage of simulations below accepted thresholds. Results were visualised using R in a scatter plot with both parameters on a separate axis. Shaded areas represented the percentage of simulations below accepted cost-effectiveness thresholds and an ellipse was added representing 80% of the simulated parameter combinations. A conventional one-way SA was performed for comparison. **RESULTS:** The one way SA found wide ranges of incremental cost-effectiveness ratios (ICER) for the intercept and slope parameters (£10,000 - £50,000 per QALY gained). The method described above found that 78% of the simulated pairs resulted in ICERs below £20,000 per QALY gained, and 93% in ICERs below £30,000. The scatter plot visualised the combined uncertainty and their impact on the ICER. A limitation is that the visualisation only allows for 2 correlated parameters. Also, the use of R to generate the graph complicates incorporation of this SA in Excel models. **CONCLUSIONS:** A method was demonstrated to show the impact of correlated parameters in cost-effectiveness analyses. This method may be especially helpful when assessing the uncertainty around parametric survival fits.